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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:
YUHPYNG L. CHEN

APPLICATION NO.: 09/580,287

FILING DATE: May 30, 2000

TITLE: CORTICOTROPIN RELEASING FACTOR ANTAGONISTS

Mail Stop
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. 1.132

Sir:

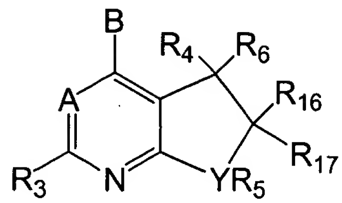
YUHPYNG L. CHEN, hereby declares, states and says that:

1. She received a B.S. from the National Cheng-Kung University in Taiwan (1975), a M.S. from Johns Hopkins University (1977), and a Ph.D. from the University of Michigan (1980).

2. She is currently employed by Pfizer Inc. as a research advisor in the Pfizer research facility in Groton, Connecticut, and she has worked at Pfizer Inc. for 21 years.

3. She is familiar with the subject matter of the above-identified application and the references cited therein.

4. The above-identified application is directed to a compound having general formula



as claimed in claim 1, to compositions containing the compound claimed in claim 1, and to methods comprising administering the compound claimed in claim 1.

5. The enclosed IC_{50} data for binding to the CRF receptor show the effectiveness of representative compounds in treating the conditions recited in the claims.

She further declares that all statements made herein of her own knowledge are true and all statements made on information and belief are believed to be true. All statements made herein are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code, and that willful false statements may jeopardize the validity of the above application or any patent that may issue from it.

Date: Nov. 20, 2003

Yuhpyng L. Chen
Yuhpyng L. Chen

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Organic Chemistry

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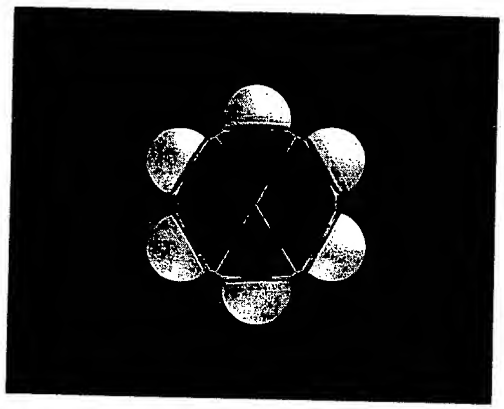
13

Aromaticity

Benzene



13.1 Aliphatic and aromatic compounds

Chemists have found it useful to divide all organic compounds into two broad classes: **aliphatic** compounds and **aromatic** compounds. The original meanings of the words "aliphatic" (*fatty*) and "aromatic" (*fragrant*) no longer have any significance.

Aliphatic compounds are open-chain compounds and those cyclic compounds that resemble open-chain compounds. Except for the occasional appearance of a phenyl (C_6H_5) group, the hydrocarbon portions of the compounds that we have studied so far have been aliphatic.

Aromatic compounds *are benzene and compounds that resemble benzene in chemical behavior*. Aromatic properties are those properties of benzene that distinguish it from aliphatic hydrocarbons. The benzene molecule is a *ring*: a ring of a very special kind. There are certain compounds—other ring compounds—which seem to differ from benzene in structure, yet which behave very much like benzene. These other compounds, it turns out, actually do resemble benzene in structure—in basic electronic configuration—and they are aromatic, too.

Aliphatic hydrocarbons—alkanes, alkenes, alkynes, and their cyclic analogs—undergo chiefly addition and free-radical substitution: addition at multiple bonds, and free-radical substitution at other points along the aliphatic chain. These same reactions, as we have seen, take place in the hydrocarbon portions of other aliphatic

compounds. The reactivity of these hydrocarbon portions is affected by the presence of other functional groups, and the reactivity of these other functional groups is affected by the presence of the hydrocarbon portions.

In contrast to aliphatic hydrocarbons, we shall find, *aromatic hydrocarbons are characterized by a tendency to undergo heterolytic substitution.* Furthermore, these same substitution reactions are characteristic of aromatic rings wherever they appear, regardless of other functional groups the molecule may contain. These other functional groups affect the reactivity of the aromatic rings, and the aromatic rings affect the reactivity of these other functional groups.

In this chapter we shall examine the fundamental quality of *aromaticity*: just how aromatic compounds differ in behavior from aliphatic compounds, and what there is in their structure that makes them different. In Chapter 14 we shall see how these characteristic aromatic reactions take place, and how they are affected by substituents on the aromatic ring. In Chapter 15 we shall take the opposite viewpoint, and look at the remarkable effects that aromatic rings, acting themselves as substituents, exert on reactions taking place in other parts of the molecule.

In the remainder of the book we shall do as organic chemists do, and deal with both aliphatic molecules and aromatic molecules as they happen to appear—or, as is commonly the case, with molecules that are *both* aliphatic *and* aromatic. It is important not to attach undue weight to the division between aliphatic and aromatic compounds. Although extremely useful, it is often less important than some other classification. The similarities between aliphatic and aromatic acids, for example, or between aliphatic and aromatic amines, are more important than the differences.

13.2 Structure of benzene

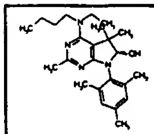
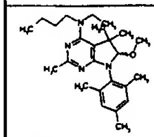
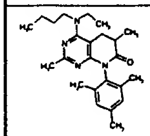
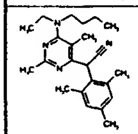
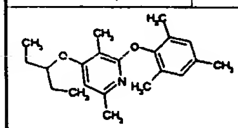
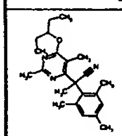
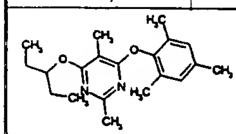
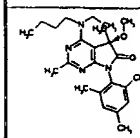
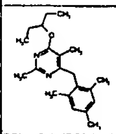
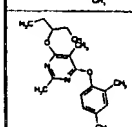
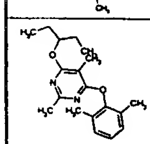
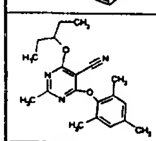
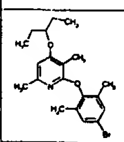
It is obvious from our definition of aromatic compounds that any study of their chemistry must begin with a study of benzene. Benzene has been known since 1825; its chemical and physical properties are perhaps better known than those of any other single organic compound. In spite of this, no satisfactory structure for benzene had been advanced until about 1931, and it was ten to fifteen years before this structure was generally used by organic chemists.

The difficulty was not the complexity of the benzene molecule, but rather the limitations of the structural theory as it had so far developed. Since an understanding of the structure of benzene is important both in our study of aromatic compounds and in extending our knowledge of the structural theory, we shall examine in some detail the facts upon which this structure of benzene is built.

13.3 Molecular formula. Isomer number. Kekulé structure

(a) *Benzene has the molecular formula* C_6H_6. From its elemental composition and molecular weight, benzene was known to contain six carbon atoms and six hydrogen atoms. The question was: how are these atoms arranged?

In 1858, August Kekulé had proposed that carbon atoms can join to one another to form *chains*. Then, in 1865, he offered an answer to the question of benzene: these carbon chains can sometimes be closed, to form *rings*. As he described it later:

	23	
	73	
	98	
	120	
	5	
	3380	
	17	
	392	
	39	
	164	
	865	
	13	
	1	